C4

54. (Amended) The composition of claim 53, wherein the enzyme is an alkaline phosphatase.

55. (Amended) The composition of claim 54, wherein the enzyme is bacterial alkaline phosphatase (BAP).

56. (Amended) The composition of claim 1, wherein the reversible linkages are different.

REMARKS

A check in the amount of $445.00 for a three-month extension of time (small entity) accompanies this amendment and response. Any fees that may be due in connection with the filing of this paper, if the attached check is in the wrong amount, improper or is missing, or with this application during its entire pendency, may be charged to Deposit Account No. 50-1213. If a Petition for an Extension of Time is required, this paper is to be considered such petition.

A Change of Address Notification accompanies this amendment and response.

Claims 1-51 and 53-56 are pending. Claims 1-20, 44-48, 50, 51 and 53-56 are amended. Basis for the amendments to the claims may be found in the claims are originally filed. No new matter is added.

REJECTION OF CLAIMS 1-51 AND 53-56 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 1-51 and 53-56 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. It is alleged that the terms "support,", "reversible linkage," and the components of the claimed subject matter are indefinite. Applicant respectfully traverses this rejection.

Relevant Law

35 U.S.C. §112, second paragraph, requires only reasonable precision in delineating the bounds of the claimed invention. The claim language is satisfactory if it reasonably apprises those of skill in the art of the bounds of the claimed invention and is as precise as the subject matter permits. *Shatterproof*

Glass Corp. v. Libby-Owens Food Co., 758 F.2d 613, 624, 225 USPQ 634 641 (Fed. Cir.), *cert. dismissed*, 106 S. Ct. 340 (1985).

The amount of detail required to be included in the claims depends on the particular invention and the prior art and is not to be viewed in the abstract, but in conjunction with whether the specification is in compliance with the first paragraph of 35 U.S.C. §112. If the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more. *Scripps clinic & Research Foundation v. Genentech Inc.* 18 USPQ 1001 (Fed. Cir. 1991).

"Support"

It is alleged that the claims are indefinite for allegedly having two definitions of "support." Instant claim 1, and claims dependent thereon, is directed to a "composition," not to a "support." It is respectfully submitted that the amendments to the claims herein have obviated this rejection. Applicant respectfully requests reconsideration and removal of this ground of rejection.

"Reversible linkage"

The Office Action alleges that the recitation of a "reversible linkage" renders the instant claims indefinite. It is urged that every linkage, including a carbon-carbon covalent bond, is reversible under some conditions. The Office Action further alleges that the conditions required for reversibility are not specified.

The claims are directed to compositions and methods of use of the compositions for (i) purification of products of nucleic acid amplification procedures, (ii) sequencing a target nucleic acid, and (iii) genetic or expression profiling. In these methods, the biopolymers of the claimed compositions are, in certain embodiments, cleaved from the insoluble support and analyzed. Thus, the reversible linkages of the instant claims are those that may be cleaved in the presence of biopolymers without affecting the structure of the biopolymers.

One of skill in the art would know which linkages are "reversible" under these conditions. The linkages are intended to bind a biopolymer to an insoluble support or to another biopolymer, and are reversible in that the biopolymer may be cleaved from the insoluble support or other biopolymer and recovered intact. One of skill in the art would be able to readily determine, using standard methods, whether a given linkage was within the scope of "reversible linkages" for use in the instant compositions and methods.

In addition, the specification provides several non-limiting examples of reversible linkages, including heterobifunctional trityl groups, hydrophobic interactions stable under aqueous conditions, photocleavable bonds, and chelate complexes (see, *e.g.*, page 3, lines 18-20, page 4, lines 3-4, page 8, lines 13-15 and 21-27, and page 9, lines 1-18). Therefore, the recitation of "reversible linkages" is not indefinite.

Components of the claimed subject matter

It is further alleged in the Office Action that the components of the claimed subject matter are indefinite. It is urged that it is unclear whether the claims are directed to compositions containing one, two, three or four basic components. It is further alleged that the claims do not specify whether these "components" can be found within the same molecule. The Office Action alleges that a single nucleic acid molecule attached to a surface can meet the limitations of the instant claims. Applicant respectfully disagrees.

The instant claims are directed to a composition containing (i) a first biopolymer linked to (ii) an insoluble support by (iii) a reversible linkage, and (iv) a second biopolymer linked to the first biopolymer by (v) a reversible linkage. Thus, the compositions of the instant claims contain five (5) components. As described in the specification, the first and second biopolymers may be the same or different (see, *e.g.*, page 6, lines 1-14) and include nucleic acids (or nucleic acid analogs/mimetics), or peptides or proteins, or small reporter molecules. The reversible linkages may be the same or different, and include

heterobifunctional trityl groups, hydrophobic interactions stable under aqueous conditions, photocleavable bonds, and chelate complexes (see, *e.g.*, page 3, lines 18-20, page 4, lines 3-4, page 8, lines 13-15 and 21-27, and page 9, lines 1-18). The insoluble supports are defined in the specification at, *e.g.*, page 5, lines 17-26, and include membranes, glass plates, metals, plastic films and composites thereof with a homogeneously functionalized surface or functionalized to result in an array format including flat supports with pits, wells, combs, microtiter plates, microtiter filter plates; the supports can also be magnetic or with an array shaped (checkered) magnetic field; the supports can also be used as beads from different plastic materials, inorganic supports such as silica, GPG (Controlled Pore Glass), metal, different polymeric material, cellulose, Sephadex, Sepharose; the beads can be porous or non-porous, of different diameter and magnetic or non-magnetic. Also a combination of beads in the pits/wells of flat supports thus forming an array format are included in the definition of insoluble support.

Therefore, the instant compositions contain five components, each of which is clearly defined in the specification. The claims are not indefinite. A single nucleic acid attached to a surface does not meet the limitations of the instant claims.

"Insoluble support"

It is further alleged that the chemical composition of the "support" is unspecified except for the allegedly broad limitation "insoluble." It is alleged that a nucleic acid is insoluble in alcohol solution, and since alcohol solutions are not excluded from the claims, "support" can be a region of a nucleic acid. Applicant respectfully disagrees. As described in detail above, the term "insoluble support" is clearly defined in the specification. A region of a nucleic acid molecule is not within the scope of this definition. Therefore, the claims are not indefinite for reciting an "insoluble support."

"Biopolymer"

It is also alleged that without more specificity of the chemical identity of the "biopolymers," the instant claims are indefinite. Applicant respectfully disagrees. The specification also provides a definition of "biopolymers" (see, *e.g.*, page 5, lines 12-16). Therefore, the claims are not indefinite for recitation of "biopolymer." Biopolymers include organic molecules, including nucleic acids, peptides and polypeptides. Thus, the claims are not indefinite because of this recitation.

"Linkages"

It is further alleged that the claims are indefinite for recitation of "linkages." As described in detail above, the linkages are reversible linkages, which may be the same or different, and include heterobifunctional trityl groups, hydrophobic interactions stable under aqueous conditions, photocleavable bonds, and chelate complexes (see, *e.g.*, page 3, lines 18-20, page 4, lines 3-4, page 8, lines 13-15 and 21-27, and page 9, lines 1-18). Therefore, the recitation of "linkages" does not render the claims indefinite.

Point of attachment of linkers on the biopolymers

The Office Action alleges that without more specificity about the points of attachment of the linker on the biopolymers, the claims are indefinite. Applicant respectfully disagrees.

One of skill in the art would know how and where to attach the reversible linkers to the biopolymers. The specification provides guidance and non-limiting examples of such points of attachment. For example, a his_6 tail may be incorporated into a protein by modifying the 3'-end of the encoding gene with six histidine codons followed by a stop codon (see, *e.g.*, page 11, lines 2-3). Alternatively, chelator or oligoimidazolyl functionality may be present at C5 of a pyrimidine base or at C8 of a purine base, and may be introduced either internally or at the 3'-end of a nucleic acid (see, *e.g.*, page 12, lines 18-25). One of skill in the art, based on the instant disclosure and the state of the art,

would know of other points of attachment of the reversible linkers. Therefore, the instant claims are not indefinite.

REJECTION OF CLAIMS 1-51 AND 53-56 UNDER 35 U.S.C. §103(a)

Claims 1-51 and 53-56 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the teachings of Monforte *et al.* (U.S. Patent No. 5,700,642). It is alleged that Monforte *et al.* teaches an insoluble support, two biopolymers and "one reversible linkage." Applicant respectfully traverses this rejection.

Relevant Law

[I]n order to establish a *prima facie* case of obviousness, there must be evidence, preferably a teaching, suggestion, incentive or inference from the cited art or in the form of generally available knowledge that one of ordinary skill would have been led to modify the relevant teaching to arrive at what is claimed. *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963).

The prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. *Stratoflex Inc. v Aeroquip Corp.*, 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). In addition, the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 USPQ 1783 (Fed. Cir. 1992).

In addition, unexpected properties must always be considered in the determination of obviousness. A compound's structure and properties are inseparable so that unexpected properties are part of the subject matter as a whole. *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963).

The instant claims

Instant claim 1 is directed to a composition, containing two biopolymers, where the first biopolymer is linked to an insoluble support by a reversible

linkage; and the second biopolymer is linked to the first biopolymer by a reversible linkage.

Claims 2-19, 44-47 and 53-56 further specify the biopolymers, reversible linkages and insoluble supports of claim 1.

Claim 20 is directed to a method for preparing the composition of claim 1. Claims 21-28 further define this method.

Claims 29-36 are directed to oligonucleotide analogs.

Claims 37 and 38 are directed to nucleoside triphosphate analogs.

Claims 39-43 are directed to recombinant protein and peptide analogs.

Claims 48-51 are directed to methods of use of the composition of claim 44.

The teachings of Monforte *et al.* and differences from the instant claims

Monforte *et al.* teaches methods of oligonucleotide sizing using immobilized cleavable primers. It is acknowledged in the Office Action that the claims differ from Monforte *et al.* in the recitation of "two biopolymers." The Office Action points to Figure 6B of the reference. This Figure illustrates an oligonucleotide 16-mer primer immobilized via a group "I" to an insoluble support, and linked through an "X" group to an oligonucleotide containing a CTGC moiety resulting from primer extension following hybridization to a target DNA:

support—I—(16-mer)—X—(CTGC-oligonucleotide)

Cleavage of the "X" group provides the CTGC-containing oligonucleotide for size analysis. The Examiner alleges that it would have been *prima facie* obvious to consider the nucleic acids on either side of the "X" as two biopolymers.

The reference does not teach or suggest that the "I" group is a reversible linkage, as required by the instant claims. "I" groups are shown in the reference in Figure 2, and do not include reversible linkages, including the trityl

derivatives, chelate complexes, hydrophobic interactions or photocleavable functionalities of the instant claims.

The instant claims are directed to biopolymers linked through two reversible linkages (I or II) to an insoluble support, *e.g.*,:
insoluble support—(I)—(first biopolymer)—(II)—(second biopolymer)

In one embodiment, cleavage of reversible linkage I following filtration to remove undesired byproducts provides a (first biopolymer)—(II)—(second biopolymer) conjugate that is analyzed. Monforte *et al.* teaches that the immobilized 16-mer primer is discarded prior to size analysis of the CTGC-oligonucleotide. Thus, the analyte in Monforte *et al.* is the CTGC-oligonucleotide, while the analyte in the instant claims is the (first biopolymer)—(II)—(second biopolymer) conjugate.

Furthermore, there would have been no motivation in Monforte *et al.* to make the "I" group a reversible linkage since the 16-mer primer is intended to be discarded prior to size analysis of the CTGC-oligonucleotide. Absent such motivation, the instant claims are not *prima facie* obvious over the teachings of Monforte *et al.*

The Office Action has failed to establish a *prima facie* case of obviousness

In order to establish a *prima facie* case of obviousness, the cited reference must provide a teaching or suggestion that would have motivated one of ordinary skill in the art to do what applicant has done. No such motivation exists in Monforte *et al.* The cited patent teaches composition containing an insoluble support, two biopolymers, and *one* reversible linkage. This reference does not teach or suggest the instantly claimed compositions containing an insoluble support, two biopolymers, and *two* reversible linkages. Nor does the reference teach or suggest modification of the compositions taught therein to arrive at the compositions of the instant claims. The reference does not teach or suggest using two reversible linkages. Nor does the reference provide any motivation to use two reversible linkages since, as described above, the 16-mer

primer of the reference is intended to be discarded prior to size analysis of a CTGC-oligonucleotide. Therefore, the compounds of the instant claims are not obvious over the teachings of Monforte *et al.*

* * *

In view of the above, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	KÖSTER *et al.*
Serial No.:	09/355,705
Confirmation No.:	6820
Filed:	November 5, 1999
For:	A REVERSIBLE STOICHIOMETRIC PROCESS FOR CONJUGATING BIOMOLECULES
Art Unit:	1656
Examiner:	Houtteman, S.

I hereby certify that this paper and the attached papers are being deposited with the United States Postal Service as First Class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231, on this date.

07/03/01
Date

Rita Jennings
Rita Jennings

ATTACHMENTS TO RESPONSE TO OFFICE ACTION

The following attachments are provided:

(1) A marked up copy of claims 1-20, 44-48, 50, 51 and 53-56 showing the amendments herein; and

(2) A Change of Address Notification.

* * *

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07/03/01
Date

Rita Jennings

MARKED UP CLAIMS (37 CFR §1.121)

Please amend claims 1-20, 44-48, 50, 51 and 53-56 as follows:

1. (Twice Amended) [An insoluble support] A composition, comprising two biopolymers, wherein:

the first biopolymer is linked to [the] an insoluble support by a reversible linkage; and

the second biopolymer is linked to the first biopolymer by a reversible linkage.

2. (Twice Amended) [The insoluble support] The composition of claim 1, wherein the two biopolymers are comprised of nucleic acids.

3. (Twice Amended) [The insoluble support] The composition of claim 1, wherein the two biopolymers are comprised of polypeptides.

4. (Twice Amended) [The insoluble support] The composition of claim 1, wherein the two biopolymers are comprised of a nucleic acid and a protein.

5. (Twice Amended) [The insoluble support] The composition of claim 1, wherein one reversible linkage is formed through a trityl derivative, a chelate complex, a hydrophobic interaction or a photocleavable functionality.

6. (Twice Amended) [The insoluble support] The composition of claim 1, wherein the insoluble support is selected from the group consisting of a flat surface, a microtiter plate, a comb and a bead.

7. (Twice Amended) [The insoluble support] The composition of claim 6, wherein the insoluble support is selected from the group consisting of a silicon wafer, glass plate, metal, plastic, film and composites thereof with pits or wells.

8. (Twice Amended) [The insoluble support] The composition of claim 7, further comprising two or more additional linked biopolymers, wherein the biopolymers are linked to the insoluble support in an array format.

9. (Twice Amended) [The insoluble support] The composition of claim 7, wherein the support comprises an inorganic material selected from the group consisting of silica, Controlled Pore Glass (CPG), plastic, metal, cellulose, agarose and dextran cross—linked with epichlorohydrin.

10. (Twice Amended) [The insoluble support] The composition of claim 6, wherein the insoluble support comprises a magnetic or electromagnetic material.

11. (Twice Amended) [The insoluble support] The composition of claim 2, wherein the nucleic acids are selected from the group consisting of deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and analogs or mimetics of DNA or RNA.

12. (Twice Amended) [The insoluble support] The composition of claim 3, wherein the polypeptides are selected from the group consisting of an antibody, enzyme, receptor and peptide.

13. (Twice Amended) [The insoluble support] The composition of claim 1, further comprising a spacer between the first biopolymer and the insoluble support.

14. (Twice Amended) [The insoluble support] The composition of claim 4, wherein the reversible linkage between the nucleic acid and the polypeptide comprises a chelate complex.

15. (Twice Amended) [The insoluble support] The composition of claim 14, wherein the chelate complex is formed by the reaction of a nucleic acid containing a chelate functionality with a polypeptide containing an imidazolyl functionality in the presence of a metal ion.

16. (Twice Amended) [The insoluble support] The composition of claim 14, wherein the chelate complex is formed by the reaction of a nucleic acid containing an imidazolyl functionality with a polypeptide containing a chelate functionality in the presence of a metal ion.

17. (Twice Amended) [The insoluble support] The composition of claim 15, wherein the polypeptide is an enzyme.

18. (Twice Amended) [The insoluble support] The composition of claim 17, wherein the enzyme is an alkaline phosphatase.

19. (Twice Amended) [The insoluble support] The composition of claim 18, wherein the enzyme is bacterial alkaline phosphatase (BAP).

20. (Twice Amended) A method for preparing [the insoluble support] the composition of claim 1, comprising the steps of:

a) immobilizing a nucleic acid to an insoluble support via a first reversible linkage; and

b) conjugating said nucleic acid with a polypeptide via a second reversible linkage.

44. (Twice Amended) [The insoluble support] The composition of claim 1, wherein:

the first biopolymer is a nucleic acid;

the insoluble support is linked via a spacer to the nucleic acid through a reversible heterobifunctional trityl group;

the second biopolymer is an enzyme; and

the nucleic acid is conjugated to the enzyme through a reversible chelate complex.

45. (Twice Amended) [The insoluble support] The composition of claim 44 in which the insoluble support is comprised of magnetic beads; the chelate complex is formed via a nitrilotriacetic acid functionality in the presence of Ni^{2+}; and the enzyme is BAP-his_6.

46. (Twice Amended) [The insoluble support] The composition claim 44 in which the insoluble support is a silicon wafer carrying the reversible functionalities to bind the nucleic acid either directly on the surface or through beads in pits or wells in an array format; the chelate complex is formed via a nitrilotriacetic acid functionality in the presence of Ni^{2+}; and the enzyme is BAP-his_6.

47. (Twice Amended) [The insoluble support] The composition of claim 44 in which the insoluble support is the filter bottom in the wells of a microtiter filter plate; the chelate complex is formed via a nitrilotriacetic acid functionality in the presence of Ni^{2+}; and the enzyme is BAP-his_6.

48. (Twice Amended) A method of purification, comprising: contacting [the insoluble support] the composition of claim 44 with products of nucleic acid amplification procedures, whereby the products are purified.

50. (Twice Amended) A method of sequencing a target nucleic acid, comprising sequencing target nucleic acid wherein nucleic acid bound to [the insoluble support] the composition of claim 44 serves as a primer.

51. (Twice Amended) A method for genetic or expression profiling, comprising contacting [the insoluble support] the composition of claim 44 with a sample comprising mRNA or cDNA, thereby detecting the identity and relative quantity of the mRNA or cDNA.

53. (Amended) [The insoluble support] The composition of claim 16, wherein the polypeptide is an enzyme.

54. (Amended) [The insoluble support] The composition of claim 53, wherein the enzyme is an alkaline phosphatase.

55. (Amended) [The insoluble support] The composition of claim 54, wherein the enzyme is bacterial alkaline phosphatase (BAP).

56. (Amended) [The insoluble support] The composition of claim 1, wherein the reversible linkages are different.

* * *

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